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Expert Panel: Selection and Sequencing HER2-Targeted Therapies for mCRC

Announcer:
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Dr. Strickler:
Hi. I'm John Strickler from Duke University Medical Center here to discuss selection and sequencing of anti-HER2 therapies in HER2 positive metastatic colorectal cancer. Joining me today is Dr. Andrea Cercek, my colleague from Memorial Sloan Kettering Cancer Center in New York. It's a pleasure to see you here today, Andrea.

Dr. Cercek:
Thanks so much for having me, John.

Dr. Strickler:
So, HER2 is an emerging target for metastatic colorectal cancer. How are you approaching HER2 positive disease differently from, say, your more standard patient with metastatic colorectal cancer?

Dr. Cercek:
So as you said, it's an emerging and important target. And so, it's something that we absolutely pay attention to when we look at our biomarkers, and we look at sequencing. So from all stage IV patients, you know, when we meet them, we get next generation sequencing. So I do sequencing for MSI, for HER2, BRAF, and RAS, and in HER2 amplified patients that are RAS wild-type, I now try to enroll them on a study targeting HER2, in the MOUNTAINEER-03 study, which I'm sure it will talk about a bit more in detail. But that's an off-the-bat important thing in terms of first-line therapy.

In later lines of therapy, if the patient, which often happens, comes to me on chemotherapy after progression on first line or second line, I also look for HER2 amplification. And in patients that are HER2 amplified and RAS wild-type, I use typically targeted monoclonal antibodies and TKI combination to target HER2. And we now have FDA approval for tucatinib and trastuzumab in that setting. And so that would be my go-to.

In patients that are RAS mutated but HER2 amplified, HER2 is still an important target. And that's where we think about the ADCs like in HER2 treatment. Once patients progress on a TKI combination, then that's another option where we can use ADCs. And that's typically my approach.

But I think, you know, for me, it's certainly a really important part of my clinical practice is looking for HER2 amplification in colorectal cancer.

Dr. Strickler:
I agree with everything you've said. And I approach it very similarly. And you and I have worked together quite a bit in researching this target. That's probably why we're so similar in terms of how we approach it.

Understanding that many of these patients have RAS wild-type microsatellite stable disease, how do you feel about treating these patients with say, an anti-EGFR therapy?

Dr. Cercek:
So we've actually seen data in preclinical models and in actual patients that anti-EGFR therapy in the presence of HER2 amplification just does not work well, so I try not to use it. You know, I would prefer other options for treatment, but I really don't use anti-EGFR therapy.

Dr. Strickler:
I agree with you. And it's increasingly a very nuanced discussion with patients, because it is technically an approved therapy for these patients that we're not giving and helping those patients to understand that there are there's this marker, it's relatively rare, it suggests resistance to standard of care therapy and suggest a better path for that patient is important.

When do you - understanding that, ideally, we will put all of our patients on a trial if we could, but sometimes patients don't enroll on a trial, they don't meet eligibility. When would you actually bring that anti-HER2 therapy to the patient? Would you, you know, assuming you get a result from your NGS profile 4 weeks after you start frontline chemo, are you going to think about introducing an anti-HER2 therapy during the first line? During maintenance? Second line? Third line? Where's that fit now?

Dr. Cercek:
That's a great question. I think for now, the data and the approvals that we have, if a patient starts on chemotherapy as first line, I would continue the chemotherapy and treat as I normally would, you know, with continuation of chemotherapy eventual, if, for example, if they're in FOLFOX, eventually stopping oxaliplatin continuing just 5-FU. And then at the time of progression, I think would be, you know, the decision point whether or not to treat with HER2 targeted therapy at that point, or continuing second-line chemotherapy and then in the refractory setting, introducing HER2 therapy. That's kind of my decision point. But absolutely at some point in this patient's treatment, either second or third line is when I would focus on HER2 targeted therapy.

The problem is - or not the problem, but the question really is, you know, the approval in the data for HER2 targeted therapy are single agent not in combination with chemotherapy. And so to start to add them to chemotherapy backbone, we're kind of deviating from what we know. Of course, that's what MOUNTAINEER-03 is going to answer for us is because it's combining HER2 targeted therapy with a FOLFOX backbone chemotherapy. But for now, I really would do it, you know, just HER2 targeted therapy, probably in the third line in my practice.

Dr. Strickler:
Yeah, this is - it's a difficult challenge for us. We now have our first FDA approved anti-HER2 regimen for HER2 positive metastatic colorectal cancer. That's, of course, tucatinib and trastuzumab, which you and I have worked with in a clinical research setting. And what we've seen from that are response rates, you know, 38% in an overall population, but among patients who are highly HER2 positive, we see even more significant benefit. And that's been shown in the past.

And I think the challenge is understanding that second-line chemotherapy, and if you just take the standard in the United States, it's probably something like FOLFIRI with a biologic, that has a response rate that's, you know, sometimes as low as 5% with FOLFIRI/bev. You know, and you've got a chemotherapy-free regimen with response rates significantly greater with great tolerability. Sometimes it gets tempting to bring that precision cancer medicine strategy up ahead of cytotoxic chemotherapy, particularly when the PFS and the response rate is so much greater than the second line standard of care. How do you feel about that?

Dr. Cercek:
No, I agree with you completely. I mean, I think that's, you know, it's certainly something to think about in it. And as you said, in these patients that are highly HER2 overexpressed or amplified, it certainly seems that their tumors are driven by this pathway. And so targeting it really helps. And as you said, the response rates, the PFS, and not only that, for me, it's also the survival benefit. In the MOUNTAINEER study of, you know, median overall survival of 24 months, we just don't see that in second or third-line therapy -

Dr. Strickler:
Yeah.

Dr. Cercek:
-ever, in metastatic colorectal cancer. And so I certainly think that, you know, it's important, and it should be done, because there clearly is a benefit in that subset of patients.

Dr. Strickler:
And the flip side of this is the patients also want this targeted therapy. They want chemotherapy-free regimens that are very precise in

how they target these tumors with a, you know, many cases a good tolerability, a good side effect profile. They're demanding this too, and we want to do it. So I think it's something where we want to bring these therapies earlier and earlier into the clinic so that patients don't have to wait till third line to get highly active well-tolerated treatment. So I think that's to your point, the MOUNTAINEER-03 trial, which is designed to bring tucatinib and trastuzumab, which is currently FDA approved for HER2 positive colorectal cancer in the third-line setting and beyond, bring it up into the frontline with standard chemotherapy. And that could change our standard of care. We'll see how the results play out but I think that's a great trial for patients if they qualify.

Dr. Cercek:
Absolutely. I agree.

Dr. Strickler:
Are there are other targets and therapies that are being investigated that are interesting that have shown promise as well?

Dr. Cercek:
You know, well my interest is in neoadjuvant. So in early stage disease and trying to optimize therapy to minimize some of the toxicity, in particular in rectal cancer where our treatment includes radiation and surgery. And you know, doing that by selecting good active biomarkers that we have good therapies for, so HER2 is one of them. So we actually have a trial now at MSK in locally advanced early-stage rectal cancer that is HER2 amplified RAS wild-type, using tucatinib and trastuzumab initially as a run-in alone and then in combination with the standard induction chemotherapy with the goal of getting those robust responses and hopefully clinical complete responses and potentially avoiding radiation and/or surgery depending on the response. So I think that'll be, you know - that'll be very exciting and very helpful, and the trial is actively accruing.

Dr. Strickler:
While you're inspiring me to call my pathologist after we have this discussion and create a rapid reflex panel so that we can find these patients.

Dr. Cercek:
Please do.

Dr. Strickler:
And then if we can't offer the trial here, we'll get them up to you so that they can get access to these therapies because I agree this is the future of medicine, precision cancer medicine. And, you know, so excited to have the first FDA approval of an anti-HER2 therapy in HER2 positive colon cancer. And there are other treatments out there that have also shown promise. So we've of course heard data about trastuzumab/deruxtecan, which is the antibody drug conjugate. And then there are other molecules in development as well that have shown promise. So I think this is a wonderful time for precision cancer medicine research and, you know, I'm looking forward to seeing the future advancements.

Dr. Cercek:
Me too. Thank you.

Announcer:
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